REMARKS

Claims 61-88 were pending in the instant application. No claims have been amended, added, or cancelled. For the Examiner's convenience, a copy of the pending claims are submitted herewith as APPENDIX A. No new matter has been added.

Applicants gratefully acknowledge the Examiner's withdrawal of all rejections and objections not maintained in the instant Final Office Action.

Rejection of claims 61-88 Under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph

The rejection of claims 61-88 under 35 U.S.C. §101 has been maintained because, according to the Examiner, "none of the utilities asserted by Applicant....can possibly be regarded as specific and credible." The rejection of claims 61-88 also stand rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "it is unclear how the skilled artisan is to use the protein." Applicant respectfully traverses these rejections.

The present invention features a novel family of secreted signaling factor proteins, the human CRSP proteins. Four family members have been identified and are described in the instant specification, namely human CRSP-1, CRSP-2, CRSP-3 and CRSP-4 (a murine homologue for CRSP-1 is also described). Applicant has described the chemical, physical and biological properties of the CRSP family of proteins in the instant specification, at least for example, at page 7, line 20 through page 9, line 30; at page 10, line 3 through page 12, line 14; and in Figure 7 which depicts the relationship between the CRSP proteins of the instant invention and the biological and functional domains of the human CRSPs. The chemical, physical and biological properties of the individual CRSP protein are further taught in the instant specification at least for example, at page 12, line 15 through page 13, line 12 as well as in Examples 1-2. Briefly, Applicants have identified a family of novel secreted soluble signaling proteins involved in modulation of development and differentiation. That the CRSP proteins are secreted soluble signaling factors is evidenced, at least in part, by the fact that the proteins

include hydrophobic signal peptides, are devoid of additional transmembrane domains, and include abundant and strongly conserved cysteine residues with potential for disulfide cross-linking. CRSP family members are characterized, in particular, by a conserved cysteine-rich region which includes at least two cysteine-rich domains. Working examples demonstrate that an exemplary family member, CRSP-1, is a secreted factor. By performing structural analysis and sequence comparison of the CRSP family members, Applicant has further identified signal sequences in additional family members, evidencing that the proteins comprise a family of secreted proteins.

The specification further teaches how to recombinantly produce the CRSP proteins of the present invention at least for example, at page 35, line 16 through page 39, line 4. Applicant further asserts that the CRSP proteins of the present invention can be used as modulators of differentiation and/or development, can be used in screening assays to identify compounds (*e.g.*, small molecule compounds) useful as modulators of development and/or differentiation, as well as to generate CRSP-specific antibodies useful for similar purposes. Applicant maintains their position that each of these proposed utilities are specific and substantial utilities, meeting the requisites of 35 U.S.C. 101.

Applicant maintains their position that the asserted utilities are specific, which is clear from the fact that the general class of molecules to which the claimed CRSP proteins belong, *i.e.*, isolated protein molecules, do not possess the specific utility ascribed to the CRSP proteins of the present invention. In particular, all recombinant proteins are not capable of being used to modulate differentiation and/or development or as targets in screens to identify such modulators. As support of Applicant's stated biological function and specific proposed utilities, Applicant draws the Examiner's attention to the fact that Xenopus and mouse proteins having homology to CRSP-3 have been reported as being important in development (see *e.g.*, References AG, BS and BT cited in the IDS filed October 26, 1998, describing such related proteins and their function in head induction). Applicant notes that these related Xenopus and mouse proteins and their role in

modulating development was described prior to Applicant's filing date (see Appendix B in the Amendment and Response filed August 17, 2000, which includes earlier printouts of the electronic GenBank records having Accession Nos. AF03043 and AF030433, in particular, the titles and annotations of the appended database records). A chicken cDNA related to CRSP-1 has been reported to be important in differentiation (*e.g.*, expression of this related cDNA correlates with the terminally differentiated state in chick lens fibers, see Reference AL cited in an IDS filed by Applicant on October 26, 1998). These CRSP proteins, as well as the instant claimed CRSP proteins are each part of a family of proteins sharing chemical, physical and biological properties as described in detail in the instant specification. Although Applicant is not relying on the cited publications to establish an activity and/or utility for the claimed nucleic acid molecules, Applicant brings these publications to the Examiner's attention to further *evidence the credibility of Applicant's prior assertions of utility*.

Likewise, Applicant maintains that the Krupnik *et al.* reference experimentally confirms Applicant's asserted activity of the CRSP proteins of the present invention as secreted modulators of development (contrary to the Examiner's previous assertion that a role for the CRSP proteins was mere "hypothesized" in Krupnik *et al.*). In particular, Applicants points the Examiner to page 311 of Krupnik *et al.* which demonstrate that hDkk-4 (the equivalent of CRSP-2) modulates head induction based on experiments in which the authors (which include the instant inventor) injected hDkk-4 mRNAs into developing *Xenopus* embryos and determines that the injected hDkk4 was capable of inhibiting Wnt-induced axis duplication.

Moreover, the utilities asserted by Applicant are not "throw away" utilities (*e.g.*, use as a food supplement or cosmetic additive). As the Examiner is aware, an applicant must provide only one credible assertion of specific utility for any claimed invention to satisfy the utility requirement. The instant application teaches a specific biological role for the CRSP proteins as well as setting forth their significance. No evidence has been made of record that Applicant's assertions regarding activities and/or utilities of the CRSP secreted factors as modulators of

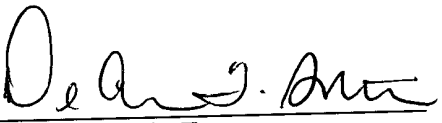
differentiation and/or development would not be considered credible to one of skill in the art. Moreover, Applicant maintains their position that the Examiner's statements of record fail to constitute a reasoned explanation as to why the utilities asserted by Applicant would not be specific and substantial. Reconsideration under 37 CFR 1.111 is requested.

CONCLUSION

In view of the foregoing amendments and following remarks, it is respectfully submitted that the application is in condition for allowance. If the Examiner has any questions or believes that a telephone conversation with Applicant's Attorney would be helpful in expediting allowance of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



DeAnn F. Smith, Esq.
Reg. No. 36,683
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Fax (617) 742-4214

Dated: **October 5, 2001**

APPENDIX A

61. A method for identifying a compound that modulates the activity of a CRSP protein, comprising:

a. providing a indicator composition comprising a protein having CRSP-2 activity;

b. contacting the indicator composition with a test compound; and

c. determining the effect of the test compound on CRSP-2 activity in the indicator composition to thereby identify a compound that modulates the activity of an CRSP-2 protein.

62. An isolated polypeptide comprising an amino acid sequence at least 80% identical to an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO:5 and the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

63. The polypeptide of claim 62, which comprises an amino acid sequence which is at least 90% identical to an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO:5 and the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

64. The polypeptide of claim 62, wherein the amino acid sequence comprises a cysteine-rich region.

65. The polypeptide of claim 62, wherein the amino acid sequence comprises a cysteine-rich domain.

66. An isolated polypeptide comprising a cysteine-rich region which is at least 80% identical to amino acids 41 to 218 of SEQ ID NO:5.

67. The polypeptide of claim 66, wherein the cysteine-rich region comprises amino acids 41 to 218 of SEQ ID NO:5.

68. An isolated polypeptide comprising a cysteine rich domain which is at least 80% identical to amino acids 41 to 90 of SEQ ID NO:5 or to amino acids 138 to 218 of SEQ ID NO:5.

69. The polypeptide of claim 68, wherein the cysteine-rich domain comprises amino acids 41 to 90 of SEQ ID NO:5 or amino acids 138 to 218 of SEQ ID NO:5.

70. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5.

71. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:5 without amino acids 1 to 19.

72. An isolated polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:4.

73. An isolated polypeptide encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:6.

74. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of incubation at 45°C in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 50°C.

75. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes to the complement of the nucleic acid molecule consisting of SEQ ID NO:4 or 6 under conditions of incubation at 45°C in 6.0 X SSC followed by washing in 0.2 X SSC, 0.1% SDS at 65°C.

76. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 80% identical to the nucleotide sequence consisting of SEQ ID NO:6.

77. An isolated polypeptide comprising an amino acid sequence which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence consisting of SEQ ID NO:6.

78. An isolated polypeptide comprising at least 10 consecutive amino acids of the amino acid sequence of SEQ ID NO:5.

79. The polypeptide of claim 78, which comprises at least 25 consecutive amino acids of SEQ ID NO:5.

80. The polypeptide of claim 79, which comprises at least 50 consecutive amino acids of SEQ ID NO:5.

81. The polypeptide of claim 80, which comprises at least 100 consecutive amino acids of SEQ ID NO:5.

82. The polypeptide of claim 81, which comprises a cysteine-rich domain of SEQ ID NO:5.

83. The polypeptide of claim 80, which comprises a cysteine-rich region of SEQ ID NO:5.

84. The polypeptide of claim 82, wherein the cysteine-rich domain comprises amino acids 41 to 90 of SEQ ID NO:5 or amino acids 138 to 218 of SEQ ID NO:5.

85. The polypeptide of claim 81, wherein the cysteine-rich region comprises amino acids 41 to 218 of SEQ ID NO:5.

86. An isolated polypeptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO:5 and SEQ ID NO:5 without amino acids 1 to 19.

87. A fusion polypeptide comprising the polypeptide of any one of claims 62, 66, 68, 72-76 and 78, operatively linked to a non-CRSP polypeptide.

88. A pharmaceutical composition comprising the polypeptide of any one of claims 62, 66, 68, 72-76 and 78 and a pharmaceutically acceptable carrier.